

# Evidence-Based Decision Making: When Should We Wait For More Information?

Coverage decisions that are conditional on gaining more evidence are a powerful tool for informed decision making.

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**ABSTRACT:** We discuss the challenge of managing innovation in and access to health care interventions in an evidence-based, cost-effective way, and we describe a decision-making framework (using U.S. and U.K. case studies) for health care payers considering the adoption of new technologies. We argue that providing reimbursement for what could be a cost-effective technology "only in the context of research" will be appropriate if the costs of delaying implementation are offset by the value of "keeping one's options open" by waiting for more information. We conclude that there is a need for better integration of health care decision-making processes with research policies. [*Health Affairs* 27, no. 6 (2008): 1642-1653; 10.1377/hlthaff.27.6.1642]

HEALTH CARE PAYERS ARE increasingly using health technology assessment to inform their decisions.<sup>1</sup> In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) was established in 1999 to develop evidence-based guidance for the National Health Service (NHS). NICE is required by statute to consider both clinical effectiveness and cost-effectiveness when making its decisions.<sup>2</sup>

In the United States, costs are not usually explicitly considered, and guidance from bodies such as the Technology Evaluation Committee of Blue Cross Blue Shield, or the Evidence-Based Practice Centers of the Agency for Healthcare Research and Quality (AHRQ) relies on clinical effectiveness information alone.<sup>3</sup> This does not mean that the U.S. health system is not subject to cost constraints; on the contrary, it contains many implicit mechanisms for rationing through reducing payment for broad groups of providers or for certain technologies.<sup>4</sup>

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The pressures for health systems across the developed world to become “early adopters” of promising new technologies have aggravated the tension between innovation and access, on the one hand, and efficiency, on the other.<sup>5</sup> However, innovations do not always represent cost-effective alternatives to current practices.<sup>6</sup> Furthermore, because of the nature of the regulatory requirements, the evidence available at an early stage of a technology’s development is often insufficient to judge long-term costs and benefits. With mounting pressure from manufacturers, patients, and clinicians for access to promising technologies as soon as they are licensed (or even earlier), how can decisionmakers be sure they are “paying for value”?

In this paper we discuss a decision-making framework that goes beyond the conventional “yes/no” coverage options, primarily by offering coverage, in certain instances, within the context of prospective studies. The framework is based on judgments of cost-effectiveness, drawing on our experience at NICE, but it can be adapted for decisionmakers who consider only comparative effectiveness.

### The Problems And Their Solutions

■ **Avoiding waste and harm.** The main problem for decisionmakers is how to balance the costs of waiting for better information against the costs of acting prematurely. If adoption is delayed, patients may be denied access to clinically important and cost-effective interventions, and incentives for research and development (R&D) investment will be reduced. Conversely, a premature decision could result in a waste of resources on cost-ineffective or even harmful practices that, once diffused, are hard to eliminate. Drug-eluting stents (DESs) are a case in point. In the United Kingdom, NICE restricted the use of DESs to patients with longer lesions or narrower vessels, for whom the benefit-harm ratio was more likely to be favorable.<sup>7</sup> In the United States, wider DES adoption may have exposed a larger proportion of patients to the initially underappreciated complication of stent-related thrombosis.

■ **Protecting the evidence base.** Premature decisions also can compromise the evidence base.<sup>8</sup> For example, further randomization might be considered unethical once a coverage decision has been made, and ongoing trials might face difficulties with recruitment of suitable patients. In addition, with reimbursement secured, sponsors of the technology will be less inclined to fund research that could narrow the indications for their technology.

Decisionmakers may sometimes wish to consider recommending limited use of the technology within the context of further evidence collection. Private U.S. plans pioneered this approach more than fifteen years ago, and the U.S. Centers for Medicare and Medicaid Services (CMS) has made a number of provisional coverage decisions that included a requirement that beneficiaries participate in a disease registry or clinical trial.<sup>9</sup> The CMS is now considering adopting a more systematic policy for linking coverage decisions with prospective data collection, known as coverage with evidence development (CED).<sup>10</sup> At the same time, new

entities, such the Center for Medical Technology Policy in California, aim to apply CED to increase the production of evidence of comparative effectiveness for public and private payers. The thinking around conditional coverage is also developing in Europe. The European Union (EU), for example, is funding a cross-national project (EUnetHTA) that is looking at ways to cover innovative technologies while generating further evidence, while the Netherlands has introduced conditional coverage arrangements for orphan and expensive inpatient pharmaceutical products. In the United Kingdom, NICE has always had the statutory right to issue recommendations for the use of a technology “only in the context of research” (OIR). This right has been exercised on a small number of occasions—in approximately 4 percent of NICE technology appraisals up to 2006.<sup>11</sup>

The availability of CED or OIR options means that coverage and research decisions can be linked. In the remainder of this paper we examine apparent conflicts between theory and the challenge of dealing with uncertainty in the real world. We put forward a decision-making framework that bridges this divide, and we discuss the broader policy implications of OIR recommendations.

### **A Proposed Decision-Making Framework**

Consider the case in which a decisionmaker has to choose between two alternative interventions (A and B) for a given group of patients, with A representing current practice and B the innovation.<sup>12</sup> A framework for making such coverage decisions includes three key questions.

■ **Question 1: Does current evidence suggest that the innovation is better than current practice?** The way in which this net-benefit question is answered varies between jurisdictions, depending on the decision criteria applied (that is, clinical effectiveness or cost-effectiveness).<sup>13</sup> From our perspective at NICE, rational decision making requires an assessment of both clinical effectiveness and cost-effectiveness. Proponents of evidence-based medicine require a systematic review with rigorous assessment of research quality, consideration of clinical and statistical significance, and a judgment about the balance between health benefits and harms before concluding that evidence is sufficient to warrant implementation of a new technology. For economists, “harms” must include the value of resources diverted from alternative uses (“opportunity cost”). The trade-off between benefits and harms can then be explored through economic evaluation and decision analysis, which suggests a rather surprising answer to the question of when evidence is sufficient to justify action.<sup>14</sup>

In decision theory, an innovation should be implemented as long as its expected net benefit (mean benefits minus mean costs) is positive.<sup>15</sup> In other words, the amount of uncertainty (or quality of the evidence) should not matter in reaching a conclusion about coverage. One argument for this approach is that large health care payers, such as the NHS or U.S. insurance companies, are protected from financial risks as a result of risk pooling and risk sharing.<sup>16</sup>

However, in real-world decision making, uncertainty and the implications of wrong decisions do matter, especially when decisionmakers adopt a “dynamic view” of the evidence base in acknowledging that their decision can affect the generation of new evidence through, for example, OIR or CED. Then the degree of uncertainty and quality of evidence become important variables to consider when making coverage decisions.

■ **Question 2: Is collection of more information worthwhile?** Having reached a decision based on the current best evidence, the decisionmaker will still need to explore whether the potential benefits of getting more information (the so-called value of information, or VOI) outweigh the costs of collecting it.

VOI takes account of both the extent of uncertainty and the size of potential impact on clinical benefits and costs.<sup>17</sup> VOI analysis weighs up four key parameters: (1) How uncertain are we about our decision? (2) What would be the impact of making the wrong decision? (This includes the effect size/magnitude of potential incremental benefit of innovation over standard practice.) (3) To what extent will the research reduce the uncertainty? (4) How much is the research likely to cost?

To help quantify the value of more information within the context of a health economic model, the following notions are used: (1) the expected value of perfect information (EVPI), which is based on parameters 1 and 2 above and provides an upper limit to the value of further perfect information; and (2) the expected value of sample information (EVSI), which also takes account of the likely reduction in uncertainty from a given research study where the information generated is likely to be less than perfect (parameter 3). If the EVSI exceeds the cost of the research (parameter 4), then the research is worth funding.

In many cases, a quantitative estimate of VOI might not be feasible, perhaps because the timing of the research or the extent of its future benefits is not known. However, a qualitative assessment of the benefits of the research in relation to its costs can still be made by considering the four parameters above in a deliberative fashion. But, as we discussed above, some decision theorists who ignore VOI would argue that one should never wait for the results of further research before implementing a change in practice whose expected benefits exceed its expected costs. However, this assumes that decisions are fully and costlessly reversible and do not affect ongoing or future research. If either of these assumptions is false, then it may make more sense to wait for more information before implementing what seems to be a cost-effective change in practice.

■ **Question 3: Should we wait for more information?** The third question (the options question) becomes relevant only after it has been established that (1) the innovation has a positive expected net benefit (“yes” to question 1), and (2) further research is worthwhile; that is, the value of information exceeds its cost (“yes” to question 2). Before recommending the innovation in this situation, decisionmakers should consider whether they should wait for additional evidence, weighing the po-

tential costs (including health benefits forgone) of delaying the implementation of an apparently promising innovation against the benefits of preventing its dissemination if this later turns out to have been a false promise. If a delay is deemed appropriate, the technology would, in the meantime, be provided only in the context of appropriate research, and current practice would continue for all other patients ("yes" to question 3). Such research arrangements need not be limited to randomized controlled trials (RCTs). It may be that the required information can be collected from a registry or prospective cohort study. This option becomes particularly appealing when the innovation has already diffused.

OIR decisions should not be made lightly: they should be considered only when adopting the innovation now would prevent worthwhile, ongoing or future, research or would incur large costs that could not be recouped if the decision were to be later reversed.<sup>18</sup> Even then, it may be better to go ahead and adopt the new technology and attempt to collect additional information alongside its use, or live with the uncertainty. The decision to delay should be based on a formal "real options" analysis, originally developed by economists to identify conditions under which it is better to wait for more information before making a financial investment, and later adapted to a health care context.<sup>19</sup> Options analysis takes account of a number of factors including the cost (in terms of health benefit forgone) of delaying the adoption of a technology that is later shown to be clinically effective and cost-effective. When considering risky decisions with irreversible consequences, there is a value in retaining the freedom to change one's mind as more information becomes available—in other words, keeping one's options open. In addition to the information provided by VOI analysis, this "options premium" depends on several questions. The first two add to the already estimated EVSI: (1) How long will the research take? (2) How likely is it that the research will be done? The next question has to do with the cost of delaying the adoption of the innovation: (3) What is the expected cost of delaying the implementation until the research results become available? The last two questions address the conditions discussed under question 3 of the framework: (4) What (irreversible) costs would be incurred if we were to implement the innovation now and to later find that it was inferior to current practice? (5) Would implementing the innovation now prevent worthwhile ongoing or future research? Options theory provides a means of weighing these various costs and the consequences of acting now versus waiting.

While VOI (question 2) helps us establish the value of collecting more information, options theory (question 3) allows us to estimate the value of waiting for this additional information before implementing our decision. If the probability of having the research done in a timely fashion is low, the forgone benefits associated with a delay will increase, and the value of delaying will be smaller.

However, quantitative estimation of the options premium may be difficult. The theory and application of options analysis is well developed for financial and man-

agerial investment decisions, but so far only rudimentary estimates of the size of the options premium have been made for health technology assessment.<sup>20</sup> Despite this, options theory provides a qualitative checklist for decisionmakers to consider before implementing an apparently beneficial new technology.

### **Application Of The Framework To Case Studies**

Here we describe the application, retrospectively and in a qualitative fashion, of our framework to case studies from the United Kingdom and the United States where OIR decisions were made.<sup>21</sup>

■ **Case study 1: Laparoscopic versus open surgery for colorectal cancer—NICE (U.K.).** In 2000 NICE reviewed the use of laparoscopic compared to open resection of colorectal cancer and recommended that the former should be used only in the context of an RCT. The limited evidence at the time suggested that the technology could be an effective and cost-effective use of NHS resources (“yes” to the net-benefit question), but there was a great degree of uncertainty around long-term effects. As a result, NICE decided that collection of further evidence would be worthwhile and encouraged surgical societies to support recruitment to an ongoing trial (“yes” to the VOI question) and delay widespread adoption of the technology (“yes” to the options question).

When the guidance was reviewed in 2006, NICE judged that there was by then sufficient evidence to conclude that laparoscopy was more cost-effective (“yes” to the net-benefit question under certain circumstances—for example, with specially trained surgeons). NICE still thought that further research would be worthwhile and called for more long-term and comparative research between laparoscopic techniques (“yes” to the VOI question). However, it did not recommend delaying introduction of the technology while this information was being collected (“no” to the options question). Had NICE issued a positive recommendation in 2000, recruitment to the then ongoing trial would have been damaged, preventing collection of valuable information on the best clinical setting for introducing this new intervention.

■ **Case study 2: Liquid-based cytology for cervical cancer screening—NICE (U.K.).** In 2000, NICE appraised liquid-based cytology (LBC) for cervical cancer screening. Available research suggested that LBC could provide important benefits and a very attractive cost-effectiveness estimate (“yes” to the net-benefit question). However, NICE concluded that there was at that time insufficient evidence to justify nationwide adoption (“yes” to the VOI question) and recommended a program of pilot projects (“yes” to the options question).

In this case, the decision to delay was based largely on concern about the costs of implementation, as well as the potential disruption to the existing national screening program. With hindsight, it might appear that NICE was too cautious, since the pilot studies produced positive findings about the value of LBC, and NICE ultimately recommended its adoption. However, the pilot studies provided

useful practical information that has assisted implementation.

■ **Case study 3: Lung volume reduction surgery for emphysema—CMS (U.S.).** Lung volume reduction surgery (LVRS) for emphysema was first introduced in the early 1990s and diffused quickly up to December 1995, when the CMS reviewed its use. The initial evidence (small case series with short-term follow-up) suggested that LVRS was a beneficial procedure (“yes” to the net-benefit question, no costs considered), but there was uncertainty over postoperative mortality. The CMS proposed further research (“yes” to the VOI question) and recommended, for the first time in its history, that the procedure be used only in the context of a clinical trial (“yes” to the options question).

Upon review in 2003, the CMS decided that it had enough information to identify patient subgroups for whom the intervention would be beneficial (“yes” to the net-benefit question for some patients). No more research was considered necessary to inform the CMS’s future review of this guidance (“no” to the VOI question). Interestingly, despite this positive coverage decision, publication of trial results, including mortality and complication rates, led to a dramatic drop in the number of eligible patients undergoing LVRS, presumably as patients and their physicians became more aware of its significant risks and limited benefits. This important safety evidence would not have become available had the CMS not used the OIR option, which probably spared many hundreds of patients from a procedure that turned out to increase their risk of death. Inappropriately forgoing the OIR option can be damaging for patients and payers.<sup>22</sup>

## Discussion

■ **Decision pathways.** Of the five decision paths resulting from our proposed framework (in the online Supplemental Exhibit 1, as in Note 12), the “only in research” (OIR) option is applied where the answer to all three questions is “yes.”<sup>23</sup> This is qualitatively different from research recommendations made to supplement coverage decisions. It is the only case where the need for further research overrules a decision to implement what is judged to be an effective/cost-effective innovation based on current best evidence.

■ **Research designs.** As noted above, the definition of *research* is not confined to RCTs. Depending on the nature of the key uncertainties, observational studies or analyses of existing databases might sometimes be sufficient. This could sometimes make OIR a feasible option in settings where randomization would be impractical, overly expensive, or inappropriate. However, nonexperimental research designs might not always be appropriate to address the key uncertainties. It is not yet clear, for example, whether the implantable cardioverter defibrillators (ICDs) or positron emission tomography (PET) scan registries initiated by a CMS CED decision will inform more-rational use of these technologies in the United States.<sup>24</sup>

■ **The ethics of delay.** For decisionmakers such as the CMS, which do not take account of costs explicitly, delaying the adoption of an apparently beneficial innova-

tion while further research is conducted may be controversial. Once a technology has been shown to be efficacious and safe through the licensing process, should it not be made available to patients? However, extrapolating from licensing data to a long-term risk-benefit balance is not always straightforward. COX-2 inhibitors, biological agents such as natazulimab, and some early statins were innovative new drugs that were made available to patients soon after marketing, only to be withdrawn on grounds of safety.<sup>25</sup> Thus, health care payers may be justified in exercising more caution than regulatory authorities. This need for caution is greater with surgical or medical devices, which usually diffuse with less strict regulatory requirements. Our framework is not a substitute for postmarketing surveillance and hardly tackles the issue of the safety of innovations; however, it could help make the trade-offs between harms (including costs where appropriate) and benefits explicit at the coverage stage.

The ethical dimension of OIR recommendations is crucially important.<sup>26</sup> In its January 2007 meeting, the NICE Citizens Council highlighted issues such as feasibility, timeliness, and value for money of the research, as well as patients' access to ongoing studies.<sup>27</sup> It considered that three key arguments provide a strong ethical grounding for OIR decisions. First, physicians and decisionmakers alike have a responsibility to acknowledge uncertainty and encourage its resolution through well-designed research; "good intentions alone have not protected patients from the unintended harmful effects of treatments."<sup>28</sup> Second, patients have a social responsibility to help reduce uncertainty.<sup>29</sup> Third, there is an openly selfish motive for participating as a patient in high-quality clinical research: patients often fare better when treated within a trial setting than when receiving the innovation outside a trial.<sup>30</sup>

■ **Equity of access to trials.** This raises potential concerns about equity of access to OIR studies, although such concerns apply also to research in the absence of OIR. In some cases—for example, if a technology register were an appropriate way of reducing uncertainty—an OIR decision need not restrict access.<sup>31</sup> However, it will often be more efficient to conduct the research on an appropriately selected sample. And, if an RCT is necessary, then only a proportion of the participants (usually half) will get access to the technology. While waiting for the research, patients might not receive potential benefits of the innovation, so there is urgency for undertaking the recommended research.

In the United Kingdom, approximately two-thirds of NICE recommendations calling for the use of a technology in the context of an appropriate research study have been (or are being) followed up through a research study. In three of these cases, recruitment for a relevant trial was under way when the NICE guidance was issued. In the remaining seven cases, the studies were set up in response to or were influenced by the NICE guidance. However, this was made possible primarily through the initiative of researchers, clinicians, sponsors, and funding organizations rather than the direct involvement of NICE in the design and funding of

the research. Only in two cases did NICE actively influence the planning and running of the trial.<sup>32</sup> However, in both cases, these discussions took place in an informal and ad hoc manner.

■ **The gap between coverage decisions and research.** For OIR recommendations to be a realistic policy option, the gap between coverage decisions and clinical research must be closed. This calls for a conceptual framework, new organizational relationships, and new approaches to setting priorities for funding of clinical research instead of relying on recruitment to relevant trials coinciding with the timing of the coverage decision. In the United Kingdom, NICE and its advisory bodies are well placed to identify and prioritize evidence gaps with important policy and practice implications. However, the expertise for formulating researchable questions and for commissioning and analyzing the studies lies outside NICE. The NHS Research and Development Programme and the Medical Research Council, both funded by the U.K. government, are NICE's natural partners. Another important partner is the technology sponsor. Both public and private funding has been used in the past to support OIR recommendations in the U.K. context. The split between public and private financing of OIR research should be considered case by case.

Only recently have NICE and the NHS agency responsible for R&D started to work together on commissioning head-to-head pragmatic research addressing the questions of NICE decisionmakers through establishing a new "direct access" to the research commissioning process.<sup>33</sup> In the U.S. setting, some of the research recommended by the CMS has been implemented by the National Institutes of Health (NIH) and the CMS. However, the lack of coordination between the major public funders of research, industry, and the CMS greatly limited the success of these initiatives.<sup>34</sup>

■ **Reconsidering in the light of new evidence.** Yet another issue has to do with the ability or willingness of the decisionmakers and payers to reconsider their original recommendations in the light of new evidence, particularly when there is disagreement over the interpretation of the data. None of the more recent CED decisions has yet produced sufficient data to support reconsideration of coverage. For example, the ICD registry is limited to baseline data mainly because of difficulties in securing sufficient funding (approximately \$3.5 million) to collect follow-up data, including device firing. At the same time, more than \$8 million per day is spent implanting ICDs across the United States.<sup>35</sup>

■ **Rewards for innovation.** Could the use of OIR recommendations have perverse long-term consequences by reducing rewards for innovation? This is an important consideration. For example, waiting for almost seven years for the research to be completed and the results published, as in the case of LVRS in the United States, would be unrealistic for most new technologies and may compromise future commercial investment in R&D. However, the time that the research is likely to take is included in calculating the options premium: the longer the duration of the research, the greater the cost of waiting before making a decision (or, equally, of putting off the

adoption of a potentially valuable technology). As discussed above, when the research is likely to take too long or is unlikely to happen at all (and such factors can be quantified in a model), then it might be better to proceed with adoption.

■ **Using the research option wisely.** OIR recommendations should certainly not be used unthinkingly to block innovations because of short-term affordability concerns. Nor should the OIR option be used as an excuse to disseminate clinically ineffective or cost-ineffective innovations under pressures from stakeholders to prevent a negative coverage decision. If properly applied, the OIR approach reduces the risk of dissemination of wasteful or harmful technologies in return for a cost of delayed implementation of some technologies that later prove to be beneficial. This should increase the incentives for research relevant to the concerns of payers and, ultimately, those of the recipients of the intervention, and differentially reward successful, rather than unsuccessful, innovation.

### Current Developments

With increasing pressure to accelerate patients' access to innovations, our proposed decision-making framework, with the option of delaying a decision until more information is available, could be a valuable tool. This model is now being considered in both the United States and the United Kingdom. A recently published review, commissioned by the U.K. Treasury to improve the impact of medical research, recommends that formal arrangements be established to "implement NICE recommendations calling on the NHS to use health interventions in a research context."<sup>36</sup> In the United States, Medicare has rechartered its coverage advisory committee to create the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC), to further develop the CED approach. In addition, efforts to expand CED to U.S. private payers have been stimulated by the Center for Medical Technology Policy, and there is growing interest among U.S. policymakers in creating a national center for comparative effectiveness research.<sup>37</sup>

The U.S. debate around comparative effectiveness research makes our proposal a very topical one. Such research is not separate from decision making; CED/OIR-type decisions form the link between the two. The focus of the current U.S. debate is, however, on developing a research infrastructure with no formal links to coverage decisions, whereby research evidence is made available for all to see, and for those willing and capable, to use. This would be the least politically sensitive option. It may also be the least effective one. Conditional coverage policies, when based on clear criteria and supported by strong implementation arrangements for data collection, are a powerful tool for making evidence-based coverage decisions. With the theoretical basis available and the commitment of most private and public decisionmakers to efficiency and evidence-based practice, this option must be reworked in the context of modern health care systems.

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## NOTES

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